AF/3738
#4 Appeal Brief
S. Burke

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	:	
	:	
Jérôme Asius et al.	:	
	:	
Serial No.: 09/242,103	:	Art Unit: 3738
	:	
Filed: February 8, 1999	:	Examiner: Prebilic Paul B.
	:	
For: IMPLANT FOR SUBCUTANEOUS OR INTRADERMAL INJECTION	:	Atty Docket: 22114/00001

APPEAL BRIEF

Commissioner for Patents
Washington, D.C. 20231

Sir:

This is an appeal from the Primary Examiner's final rejection of claims 21-35 and 37-41.

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TABLE OF AUTHORITIES

Cases

I. Real Party in Interest

The real party in interest is Aventis Pharmaceuticals Holdings, Inc. An assignment has been recorded at Reel 013439, Frame 0447.

II. Related Appeals and Interferences

There are no other appeals or interferences known to Appellant, Appellant's legal representative, or Assignee which will directly affect or be directly affected by or have a bearing on the Board's Decision in this Appeal.

III. Status of Claims

Claims 1-52 were entered in the application.

Claims 1-20 were previously cancelled without disclaimer.

Claims 21-35 and 37-41 were rejected and are the subject of this appeal.

Claims 36 and 42-53 were subject to restriction and were withdrawn from consideration. Our After Final Response, filed January 30, 2003, traversed the restriction. Withdrawn claims are attached as Appendix II.

IV. Status of Amendments

The amendments to the claims after Final Rejection, filed January 30, 2003, have been entered.

V. Summary of Invention

The present invention relates to an implant for subcutaneous or intradermal injection, intended for human administration. The present invention is intended for

reparative and/or plastic surgery and in esthetic dermatology, for filling skin cracks, fine lines, wrinkles, and gums. (Page 1, lines 1-8).

The present invention relates to microspheres, or microparticles, suspended in a gel. (Page 3, lines 2-3). An aspect of the present invention is to avoid the problems associated with the prior art. In particular it is an aspect of the present invention to avoid the inflammation, infection, and allergic reactions often associated with prior art implants such as collagen. (Page 1, line 11- page 2, line 1 and page 2 lines 17-19).

The present invention makes it possible to avoid the use of those man-made materials associated with adverse biological reactions. Silicone gel (or oil) is to be avoided because silicone is frequently the cause of chronic inflammation, granulomae, and tardive allergic reactions. (Page 1, lines 14-17). Teflon pastes are to be avoided because they are associated with chronic infection. (Page 1, lines 19-22). Bioplastique™ (Bioplasty, Inc. St. Paul, MN) is known to the prior art as a product of polymerized silicone dispersed in a polyvinylpyrrolidone matrix. This material is associated with chronic inflammation and rejection reactions. (Page 2, lines 7-11).

The inventive implant comprises microparticles or microspheres suspended in a gel. Each component of the inventive implant is selected to be hypoallergenic and to be free from other adverse biological and tissue reactions.

An aspect of the present invention provides microspheres manufactured from neutral polymers, such as polylactic acid (PLA) and polylactic-glycolic acids (PLAGA) chosen both for their innocuousness and for the pharmaceutical industry's extensive experience using these materials. (Page 3, line 10 - page 4 line 7.).

The implants of the present invention are injectable, which is achieved by suspending the microspheres or microparticles in a gel. (Page 3, lines 2-9). As is known to persons of skill in the pharmaceutical arts, injectability relates to the ability of a given formulation to pass through a syringe needle.

VI. Issues

1. Has the Examiner established, under 35 U.S.C § 102(e), that claims 21, 24, 27-31, 34-35, and 37-40 are anticipated by Ron (US 5,559,897).

2. Has the Examiner established, under 35 U.S.C § 103(a), that claims 26 and 32-33 are unpatentable over Ron (US 5,559,897).

3. Has the Examiner established, under 35 U.S.C § 103(a), that claims 21-25 and 30-31 are unpatentable over Scopelianos (EP 0711794) in view of Orly (WO 93/13755).

4. Has the Examiner established, under 35 U.S.C § 103(a), that claim 41 is unpatentable over Ron (US 5,559,897) in view of Sander (US 5,356,629).

VII. Grouping of Claims

A provisional election to prosecute Group I, claims 21-35 and 37-41, has been made. The Group I claims stand or fall together.

Group II, claims 36 and 42-52 stand as withdrawn from consideration.

VIII. Appellant's Arguments

1. Ron et al. fails to anticipate claims 21, 24, 27-31, 34, 35, and 37-40.

The Office Action, at pages 5-7, rejected claims 21, 24, 27-31, 34, 35, and 37-40 under 35 U.S.C. § 102(e), as allegedly being anticipated by Ron et al. (U.S. Pat. No. 5,597,897). Ron et al. fails to anticipate the present invention because Ron does not disclose explicitly or inherently each claim element of the present invention.

Claim 21 recites, in pertinent part, a "bioresorbable injectable implant for human administration consisting essentially of: bioresorbable microspheres or microparticles suspended in a gel..." Ron is silent as to a gel. The present invention recites carboxymethylcellulose (CMC) as a gel-forming agent. Ron recites CMC, but not as a

gelling agent. Rather, Ron uses CMC as an "osteogenic protein-sequestering agent". (Column 2, line 22). The fact that the use of a gelling agent has not even been considered by Ron et al. is emphasized by the fact that many of the disclosed sequestering agents are not considered to be suitable gelling agents.

The Examiner argues anticipation by inherency. The Examiner asserts that because Ron et al. use CMC in the same concentration as the Applicant, the physical properties of Ron et al.'s implant must be the same as that of the claimed invention.

Ron et al. fails to even remotely suggest a gel, much less an injectable gel. Ron is silent as to the use of a gel as a vehicle. A gel is defined as "a colloid in which the disperse phase has combined with the continuous phase to produce a jelly-like product." Hawley's Condensed Chemical Dictionary 555 (12th Ed. 1993). The specification of Ron et al. teaches that their implant is "a malleable (putty-like) composite...that handles appropriately for surgical implantation into an injury site." (column 4, line 66 – column 5, line 1). One of ordinary skill in the art understands the definition of "gel," and would never consider a "putty-like" composition to fall within that definition. Moreover, the composition of Ron et al. would obviously not be suitable for injection into a patient as recited in the claimed invention. The material of Ron is a substitute for bone wax: the "porous particles may also be used in combination with a sequestering agent as a substitute for bone wax at the site of a bony injury to act as a bioerodable hemostat." (Column 6, lines 19-22). Bone wax is a malleable putty-like material that a surgeon shapes with his/her hands and instruments to emplace at a site of bone injury. (See Appendix V: Bone Wax, http://www.uscneurosurgery.com). Ron discloses a malleable, putty-like material suitable as bone wax. A malleable, putty-like materials suited as bone wax is not inherently either a gel, or inherently injectable.

The Office action essentially argues that the physical properties of the entire composition, composed of multiple elements, are inherent features of a single component of that composition and not influenced by any of the other components. Further, it is argued that Ron et al. may have considered sequestering agents as gelling agents since

one of the many sequestering agents is utilized by the claimed invention as a gelling agent. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *Continental Can Co. U.S.A., Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (emphasis added). Inherency requires that the recited results or structure must necessarily be obtained, not merely that it might be achieved. See *Electra Medical Systems S.A. v. Cooper Life Sciences, Inc*, 32 U.S.P.Q.2d 1017 (Fed. Cir. 1994); *In re Oelrich*, 212 U.S.P.Q. 323 (C.C.P.A. 1981) and *In re Rebertson*, 49 U.S.P.Q.2d 1949 (Fed. Cir. 1999). Applicants suggest that the physical properties (i.e., gelatinous nature) of multi-component compositions are defined by the properties of all components and not one single component. Moreover, the physical properties of a given composition in the presence of one set of compounds will not necessarily be the same in the presence of a second set of compounds.

In the Office Action it is assumed that since Ron et al. allegedly utilizes a similar concentration of CMC in their "putty-like" implant, that the physical characteristics of that composition MUST be similar to the claimed composition. This is wrong as a matter of science and as a matter of law. As a matter of science, a person of skill in the pharmaceutical arts would recognize that similar concentrations of various CMC species do not necessarily have similar physical characteristics. For example, The Aldrich Handbook of Fine Chemicals and Laboratory Equipment, 2003-2004, discloses, at page 392, (Appendix VI: Aldrich Handbook) various carboxymethyl cellulose products. A CMC, catalogue number 36,038-4, is disclosed for which a 4% aqueous solution has a viscosity of 10-55 cps. A CMC, catalogue number 32,306-3, is disclosed for which a 1% aqueous solution has a viscosity of 3000-6000 cps. In other words, normalized for concentration, various carboxymethyl cellulose solutions may have up to at least a 2400-fold variation in viscosity. As a matter of law, the Examiner is effectively taking judicial notice of the assumption that since Ron et al. allegedly utilizes a similar concentration of CMC in their "putty-like" implant, that the physical characteristics of that composition

MUST be similar to the claimed composition. The rule permitting the taking of judicial notice is construed narrowly. "Assertions of technical facts in areas of esoteric technology must always be supported by citation to some reference work recognized as standard in the pertinent art." *In re Pardo*, 214 U.S.P.Q. 673, 677 (C.C.P.A 1982). "Allegations concerning specific 'knowledge' of the prior art, which might be peculiar to a particular art should also be supported and the appellant ...given the opportunity to make a challenge." *In re Pardo*, 214 U.S.P.Q. 673, 677 (C.C.P.A 1982). The Examiner has merely asserted the properties of CMC without citation. In addition to CMC, Ron et al.'s implant composition contains protein and large, porous particles, neither of which is present in the claimed invention. It is incorrect to assume that two different multi-component compositions will have the same physical properties simply because of a single common element.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. See *Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), cert. denied, 465 U.S. 1026 (1984). Ron et al. is silent as to a gel and therefore, cannot expressly disclose an injectable gel. The physical properties of CMC-containing compositions vary greatly dependent on, among other variables, the nature of substances admixed therein. Therefore, the physical properties of compositions containing CMC are not an inherent function of merely the CMC concentration. Therefore, Ron cannot and does not inherently anticipate the above claims.

Claim 24

It is further asserted that the range of "about 150-850 microns" recited by Ron et al. falls within the claimed range of 5 to less than 150. Applicants respectfully disagree. The present invention relates to particles having a diameter greater than 5μ,and preferably greater than 20μ, so as not to be absorbed by macrophages. (Page 3, lines 4-5). A further aspect requires the microspheres to have a diameter less than 150μ and preferably less

than 40μ so that the implant is readily injectable through a fine needle. The upper limit on the diameter also relates to avoidance of a feeling of a granular mass when the area surrounding the injection site is touched with a finger. (Page 3, lines 5-9). However, claim 24 depends from claim 21. As stated above, Ron et al. does not disclose all the elements of claim 21, and therefore cannot anticipate claim 24, which depends therefrom.

Claim 30 and 31

In the Office Action it is argued that, although there is no specific recitation of specific viscosity in the disclosure of Ron et al., because the molecular weight of the polymer used by Ron et al. is allegedly similar to that used in the claimed invention, the viscosity MUST be the same. As discussed above, and as disclosed in the Aldrich Handbook, CMC solutions, of equal concentration, may vary by up to 2400-fold in their viscosity. Moreover, claims 30 and 31 both depend from claim 21. As stated above, Ron et al. does not disclose all of the elements of claim 21, and therefore cannot anticipate claims 30 and 31, which depend therefrom.

Claim 36

In the Office Action it is further argued that example 4 of Ron et al. anticipates claim 36 of the present invention for reasons that are not explicitly stated. Applicants respectfully disagree with this assertion. However, claim 36 depends from claim 21. As stated above, Ron et al. does not disclose all of the elements of claim 21, and therefore cannot anticipate claim 36, which depends therefrom.

Claims 36-40

Finally, it is asserted that claims 36-40 are anticipated by Ron et al., because Ron et al. allegedly disclose the use of appropriate surfactants in their implant composition.

Applicants respectfully disagree with this assertion. However, claims 36-40 depend from claims 21 and 37. As stated above, Ron et al. does not disclose all the elements of claims 21 or 37, and therefore can not anticipate claims 36-40, which depend there from.

For the reasons stated above, Applicants submit that Ron et al., does not disclose all of elements of the claimed invention. As such, the rejection of claims 21, 24, 27-31, 34, 35, and 37-40, under 35 U.S.C. § 102(e), is improper. Reconsideration and withdrawal of this rejection are respectfully requested.

2. Ron et al. fail to render obvious Claims 26, 32 and 33.

In the Office Action at pages 7 and 8, claims 25, 32 and 33 have been rejected, under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ron et al. (U.S. Patent No. 5,597,897). Ron et al. fails to render obvious claims 26, 32 and 33.

Claim 26

It is argued that claim 26 is obvious over Ron et al. because biodegradation time is allegedly a function of molecular weight, hence, it would have been obvious for one of ordinary skill in the art to alter biodegradation time in order to allow for natural tissue replacement in different parts of the body.

In rejecting a claim under 35 U.S.C. § 103(a) a prima facie case of obviousness must be established. In order to do so the following burdens must be satisfied. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine referenced teachings to obtain the claimed invention. See *In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Second, there must be a reasonable expectation of success. See *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). And finally, the prior art references must teach or suggest all of the claim limitations. In the present case, none of the burdens have been satisfied.

A preferred aspect of the present invention is controlled bioresorption. In view of the implant as a foreign body, a non-resorbable implant is to be specifically avoided. (Page 2, line 38 - page 3, line 1). A preferred aspect of the present invention provides that the inventive implant is hydrolyzed and absorbed by the human body over the course of a controllable and predictable time. Preferably, the rate of bioadsorption must neither be too slow nor too fast. According to a preferred aspect of the present invention, the sorption rate of the constituent materials is such as to cause the implant to be absorbed over a period of between 1 and 3 years. (Page 2, lines 33-35). Silicone is known not to be biodegradable, its sorption rate is too slow to be absorbed over the preferred period of between 1 to 3 years as recited in claim 26. Silicone, therefore, is to be avoided on these grounds as well. (Page 1, lines 17-18). Fatty cells, derived from the patient, are absorbed and disappear within a few weeks, much faster than the preferred of 1 to 3 years. (Page 1, lines 32-36).

Nowhere in the disclosure of Ron et al. do the inventors suggest or contemplate the modification of their compositions and methods for the purpose of allowing for natural tissue regeneration in areas other than osteogenic regeneration. Even if such a suggestion were present, there would be no reasonable expectation of success in producing the claimed compositions due to the differences between the compositions of Ron et al. and the claimed invention. More specifically, Ron et al. does not teach all of the claim elements of claim 21, from which claim 26 depends. For example, Ron et al. does not expressly or inherently disclose either the presence of an injectable gel composition. Moreover, claim 21 recites, in pertinent part: "a gel consisting essentially of materials of non-animal origin. The composition disclosed by Ron does not consist essentially of materials of non-animal origin because Ron recites osteogenic proteins. No references have been cited that cure the deficiencies of Ron et al., and as such, this reference does not establish a prima facie case of obviousness over claim 26 of the present application.

Claim 32 and 33

It is further argued that claims 32 and 33 are rendered obvious by Ron et al. due to the inherent properties present in Ron et al.'s composition. As mentioned above, in order to establish a case of obviousness under 35 U.S.C. § 103(a), the cited reference(s) much contain all of the claim elements. As mentioned previously, Ron et al. does not teach all of the claim elements of claim 21, from which claims 32 and 33 depend. For example, Ron et al. does not expressly or inherently disclose either the presence of an injectable composition, nor does the disclosed composition consist essentially of materials of non-animal origin. No references have been cited that cure the deficiencies of Ron et al., and as such, this reference does not establish a prima facie case of obviousness over claims 32 and 33 of the present application.

3. Scopelianos and Orly fail to render obvious claims 21-25 and 30-31.

In the Office Action at page 8, claims 21-25 and 30-31 have been rejected under 35 U.S.C. § 103(a), as being obvious over Scopelianos et al. (EP 0711794) in light of Orly et al. (WO 93/13755). (As discussed during the January 2003 interview, apparently, the examiner intended to rely upon EP 0711 548 to Scopelianos et al.) These cited references fail to render obvious claims 21-25 and 30-31.

As appreciated by the Examiner, Scopelianos et al. fails to suggest a gelation material. This deficiency is allegedly cured by Orly et al.

In order to establish a prima facie case of obviousness under 35 U.S.C. § 103(a), it must be shown that all claim elements are present in the cited references, and moreover, a motivation to combine those references and a reasonable expectation of success once the references are combined must be established. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). See *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case this has not been done.

Scopelianos suggests a injectable microdispersion made of ε-caprolactone polymers and not polylactic or polyglycolic polymers as recited in the above claims. Scopelianos relates to ε-caprolactones and other monomers excluded by the claim 21 recitation: "microparticles consisting of at least one polymer of non-animal origin selected from the group consisting of lactic acid polymers, glycolic acid polymers, and lactic acid-glycolic acid co-polymers. Moreover, Scopelianos teaches away from the use of polylactic polymers in column 2, lines 10-25, where he states:

> Soft tissue repair or augmentation has also been proposed using lactic acid based polymer blends of amorphous oligomers with crystalline oligomers or polymers.... However, these blends do not appear to be suitable for use as injectable soft tissue defect fillers, because they are too viscous to be injected through a needle which significantly limits the utility of these blends.

Scopelianos further teaches away from a gel since the injectable composition according to Scopelianos must be low viscosity (The lacti-glycolic copolymers are "too viscous to be injected through a needle.") (See above and EP0711548B1, page 3, last paragraph). Teaching away from the invention is a *per se* demonstration of nonobviousness. *U.S. v. Adams*, 338 U.S.39, 148 U.S.P.Q. 479 (1966). Orly does not cure these deficiencies because adding a gelling agent, as suggested by Orly, would be contrary to the teachings of Scopelianos et al. Moreover, The "viscous biocompatible carrier solution" suggested by Orly et al. consists of collagen and glycosaminoglycan compositions, both of which are of animal origin. Therefore, the combination of Scopelianos and Orly does not teach all the elements of the claimed invention.

Further, Scopelianos does not suggest the use of animal-based viscous biocompatible carrier solutions, and there would be no motivation to combine the two teachings. Moreover, utilizing the combined teachings of Scopelianos, which teaches away from the use of lactic acid polymers and utilizes ε-caprolactone for injectable microdispersions, with Orly et al., which teaches the use of animal-based viscous biocompatible carrier solutions, would not result in a reasonable expectation of success in generating the bioresorbable injectable implant of the claimed invention.

As such, a prima facie case of obviousness has not been established. Reconsideration and withdrawal of the rejection of claims 21-25 and 30-31 under 35 U.S.C. § 103(a) over Scopelianos et al. and Orly et al. are respectfully requested.

4. Ron et al. combined with Sanders et al. fails to render obvious Claim 41.

In the Office Action, at page 8, claim 41 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ron et al. in view of Sander et al. (U.S. 5,356,629).

The Office Action states that Ron et al. teaches all the limitations of claim 41, and implicitly claim 37, from which claim 41 depends, except for the use of surfactant, which is allegedly cured by Sander et al.

As discussed above, at a minimum, Ron et al. fails to disclose the presence of an injectable implant that consists essentially of materials of non-animal origin as recited by the claimed invention. Sander et al. teaches the use of surfactants in moldable implants, which are not capable of being injected. Therefore, the combination of Ron et al. and Sander et al. does not contain all the elements of the claimed invention. Even if, arguendo, Sander et al. did teach the use of the claimed surfactant in an injectable implants, it would not cure the defects of Ron et al.

The combination of Ron et al. and Sander et al. does not contain all the elements of the claimed invention, and as such, does not render the claimed invention obvious. Reconsideration and withdrawal of this rejection of claim 41 under 35 U.S.C. § 103(a) over Ron et al. and Sander et al. are respectfully requested.

Nowhere in the disclosure of Ron et al. do the inventors suggest or contemplate the modification of their compositions and methods for the purpose of allowing for natural tissue regeneration in areas other than osteogenic regeneration. Even if such a suggestion were present, there would be no reasonable expectation of success in producing the claimed compositions due to the differences between the compositions of Ron et al. and the claimed invention. More specifically, Ron et al. does not teach all the

claim elements of claim 21, from which claim 41 depends. For example, Ron et al. does not expressly or inherently disclose either the presence of an injectable gel composition, nor does the disclosed composition consist essentially of materials of non-animal origin the claimed invention. No references have been cited that cure the deficiencies of Ron et al., and as such, this reference does not establish a prima facie case of obviousness over any of the claims of the present application.

The mere fact that prior art may be modified in the manner suggested by the Examiner does not make this modification obvious, unless the prior art suggests the desirability of the modification. No such suggestion appears in the prior art in this matter. The Board's attention is kindly directed to *In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984), *In re Laskowski*, 10 USPQ2d 1397 (Fed. Cir. 1989) and *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992).

Concerning the above rejection of the claims, the Board should be mindful of the following cautionary statement made by the Court in *Grain Processing Corp. v. American Maize-Products Corp.*, 5 USPQ2d 1788 (Fed. Cir. 1988):

> Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the same result of the claims in suit.

Likewise, as stated by the court in *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543 (Fed. Cir. 1985):

> It is error to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a blueprint. When prior art references require selected combination to render obvious a subsequent invention, there must be some reason for the combination, other than the hindsight obtained from the invention itself. It is critical to understand the particular results achieved by the new combination.

In the present situation, no such reasoning for the combination exists in the prior art, and nothing in the prior art would suggest the properties achieved by the present invention. Also, see *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988) wherein the Court stated that "one cannot use hindsight reconstruction to pick and choose among isolated

disclosures in the prior art to deprecate the claimed invention." Moreover, it is important to keep in mind that statements in the prior art should not be read out of context when evaluating obviousness. See *In re Wright*, 9 USPQ2d 1649 (Fed. Cir. 1989).

The prior art lacks the necessary direction or incentive to those of ordinary skill in the art to render a rejection under 35 U.S.C. 103 sustainable. The prior art fails to provide the degree of predictability of success of achieving the properties attained by the present invention needed to have a rejection under 35 U.S.C. 103 sustained. See *In re Mercier*, 187 U.S.P.Q. 774 (CCPA 1975) and *In re Naylor*, 152 U.S.P.Q. 106 (CCPA 1966).

Moreover, the properties of the subject matter and improvements which are inherent in the claimed subject matter and disclosed in the specification are to be considered when evaluating the question of obviousness under 35 USC § 103. See *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990), *In re Antonie*, 195 U.S.P.Q. 6 (CCPA 1977), *In re Estes*, 164 U.S.P.Q. 519 (CCPA 1970), and *In re Papesch*, 137 U.S.P.Q. 43 (CCPA 1963).

No property can be ignored in determining patentability and comparing the claimed invention to the prior art. Along these lines, see *In re Papesch*, supra, *In re Burt et al.*, 148 U.S.P.Q. 548 (CCPA 1966), *In re Ward*, 141 U.S.P.Q. 227 (CCPA 1964), and *In re Cescon*, 177 U.S.P.Q. 264 (CCPA 1973).

Conclusions

The above discussion renders it abundantly clear that the Primary Examiner erred in finally rejecting claims 1-42 and 45-47. Therefore, the undersigned respectfully requests the Board to reverse the Examiner and grant claims 21-52.

Respectfully submitted,

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APPENDIX I
CLAIMS ON APPEAL

21. A bioresorbable injectable implant for human administration consisting essentially of:

bioresorbable microspheres or microparticles suspended in a gel consisting essentially of materials of non-animal origin,

said microspheres or microparticles consisting of at least one polymer of non-animal origin selected from the group consisting of lactic acid polymers, glycolic acid polymers, and lactic acid-glycolic acid co-polymers.

22. The injectable implant for human administration, according to claim 21, wherein said microspheres or microparticles are present in said gel at a concentration of from 50 to 300 g/l.

23. The injectable implant for human administration, according to claim 21, wherein said microspheres or microparticles are present in said gel at a concentration of from 60 to 200 g/l.

24. The injectable implant for human administration, according to claim 21, wherein said microspheres or microparticles have a mean diameter of from 5 to less than 150 micrometers.

25. The injectable implant for human administration, according to claim 21, wherein said microspheres or microparticles have a mean diameter of from 20 to 80 micrometers.

26. The injectable implant for human administration, according to claim 21, wherein said microspheres or microparticles are bioresorbable within a period of 1 year to 3 years.

27. The injectable implant for human administration according to claim 21, wherein said microspheres or microparticles consists of a polymer selected from the group consisting of poly-L-lactic acid, poly-D-lactic acid and mixtures thereof.

28. The injectable implant for human administration, according to claim 21, wherein said polymer has a molecular mass of between 70,000 and 175,000 Daltons.

29. The injectable implant for human administration, according to claim 21, wherein said polymer has a molecular mass of between 120,000 and 170,000 Daltons.

30. The injectable implant for human administration, according to claim 21, wherein said polylactic acid has an intrinsic viscosity of between 3 and 4 dl/g.

31. The injectable implant for human administration, according to claim 21, wherein said polylactic acid has an intrinsic viscosity of between 3.35 and 3.65 dl/g.

32. The injectable implant for human administration, according to claim 21, wherein said polylactic acid has a percentage of residual monomer < 0.1%.

33. The injectable implant for human administration, according to claim 21, wherein said polylactic acid has a percentage of residual solvents< 0.01%.

34. The injectable implant for human administration, according to claim 21, wherein said gel consists essentially of water and 0.1 to 7.5% by weight carboxymethylcellulose (CMC) or hydroxypropylmethylcellulose (HPMC).

35. The injectable implant for human administration, according to claim 21, wherein said gel consists essentially of water and 0.1 to 5.0% by weight carboxymethylcellulose (CMC) or hydroxypropylmethylcellulose (HPMC).

37. A bioresorbable injectable implant, free of materials of animal origin, for human administration comprising:

microparticles, free of materials of animal origin, comprising:

at least one polymer selected from the group consisting of lactic acid polymers, glycolic acid polymers, lactic acid-glycolic acid co-polymers, and mixtures thereof; and

a gel, free of materials of non-animal origin, comprising:

water for injection,

from about 0.1 to about 7.5% (wt/wt) of an injectable gelling agent, and

a surfactant,

wherein said microparticles are suspended in said gel, and

wherein said gel is resorbable within about two months.

38. The bioresorbable injectable implant according to claim 37, wherein said gelling agent is a cellulose derivative.

39. The bioresorbable injectable implant according to claim 38, wherein said cellulose derivative is at least one member selected from the group consisting of carboxymethylcellulose and hydroxypropylmethylcellulose.

40. The bioresorbable injectable implant according to claim 37, wherein said gelling agent is synthetic hyaluronic acid.

41. The bioresorbable injectable implant according to claim 37, wherein said surfactant is at least one member selected from the group consisting of polyoxyethylene sorbitan monooleate and polyoxypropylene block copolymer surfactant.

APPENDIX II
CLAIMS SUBJECT TO RESTRICTION

36. The product obtained by freeze-drying the injectable implant for human administration according to claim 21, wherein said product is capable of reconstituting an injectable implant for human administration upon addition of water for injection.

42. A freeze-dried material which when mixed with water reconstitutes a bioresorbable injectable implant, free of materials of animal origin, for human administration, said freeze-dried material comprising:

microparticles comprising:

at least one polymer selected from the group consisting of lactic acid polymers, glycolic acid polymers, lactic acid-glycolic acid co-polymers, and mixtures thereof; and

a composition that forms a gel when mixed with water comprising:

a cryoprotecting agent;

a gelling agent, and

a surfactant.

43. The freeze-dried material according to claim 42 wherein said cryoprotecting agent is apyrogenic mannitol.

44. A method of making a bioresorbable injectable implant free of materials of animal origin consisting essentially of:

a) providing polymer microspheres or microparticles consisting of at least one polymer selected from the group consisting of lactic acid polymers, glycolic acid polymers, and lactic acid-glycolic acid co-polymers;

b)providing a gel capable of suspending said microspheres or microparticles, wherein said gel consists essentially of:

water for injection;

from about 0.1 to about 7.5% (wt/wt) of an injectable gelling agent; and

a surfactant,

c)dispersing said microspheres or microparticles in said gel at a proportion of from about 50 to about 300 grams of microspheres or microparticles per liter of gel;

d) packaging said dispersion into sterilizable, sealable containers; and

e)sterilizing said container.

45. The method of making a bioresorbable injectable implant free of materials of animal origin according to claim 44, wherein said gelling agent is at least one member selected from the group consisting of a cellulose derivative, a synthetic hyaluronic acid, a lactic acid ester, and a caproic acid ester.

46. The method of making a bioresorbable injectable implant according to claim 45 wherein said cellulose derivative is at least one member selected from the group consisting of carboxymethyl cellulose and hydroxypropylmethyl cellulose.

47. A syringe containing a unit dosage form of a bioresorbable injectable implant free of material of animal origin suitable for administration to a human patient in need thereof said implant consisting essentially of:

polymer microspheres or microparticles consisting of at least one polymer selected from the group consisting of lactic acid polymers, glycolic acid polymers, and lactic acid-glycolic acid co-polymers; and

a pharmaceutically acceptable gel capable of suspending said microspheres or microparticles, wherein said gel consists essentially of:

water for injection;

from about 0.1 to about 7.5% (wt/wt) of an injectable gelling agent; and

a surfactant.

48. A vial containing a unit dosage for of a bioresorbable injectable implant free of materials of animal origin suitable for administration to a human patient in need thereof said implant consisting essentially of:

49. A vial containing a freeze-dried material which when mixed with water reconstitutes a unit dosage of a bioresorbable injectable implant, free of materials of animal origin, suitable for administration to a human patient in need thereof said freeze-dried material comprising:

microparticles comprising:

at least one polymer selected from the group consisting of lactic acid polymers, glycolic acid polymers, lactic acid-glycolic acid co-polymers, and mixtures thereof; and

a composition that forms a gel when mixed with water comprising:

a cryoprotecting agent;

50. A method of making a freeze-dried material for reconstitution as a bioresorbable injectable implant suitable for administration to a human patient in need thereof consisting essentially of:

providing microparticles or microspheres consisting of at least one polymer selected from the group consisting of lactic acid polymers, glycolic acid polymers, and lactic acid-glycolic acid co-polymers;

providing a freeze-drying medium consisting essentially of:

a gelling agent free of materials of animal origin,

a cryoprotecting agent,

a surfactant, and

water for injection;

sterilizing said medium;

mixing about 100mg of said microparticles or microspheres with about 1.0 gram of said freeze-drying medium;

homogeneously dispersing said mixture; and

freeze-drying said dispersion.

51. A kit consisting essentially of:

a vial containing an amount of freeze-dried material which upon addition of water for injection is capable of reconstituting a unit dosage of a bioresorbable injectable implant, free of materials of animal origin, suitable for administration to a human patient in need thereof, said freeze-dried material consisting essentially of:

microspheres or microparticles consisting of at least one polymer selected from the group consisting of lactic acid polymers, glycolic acid polymers, and lactic acid-glycolic acid co-polymers; and

a composition that forms a gel when mixed with water consisting essentially of:

a cryoprotecting agent;

a gelling agent; and

a surfactant;

and an ampule containing a unit dosage of said water for injection.

52. A kit consisting essentially of :

a two-compartment syringe wherein:

a first compartment contains an amount of freeze dried material, which upon addition of water for injection is capable of reconstituting a unit dosage of a bioresorbable implant, free of materials of animal origin, suitable for administration to a human patient in need thereof, said freeze-dried material consisting essentially of:

microspheres or microparticles consisting of at least one polymer selected from the group consisting of lactic acid polymers, glycolic acid polymers, and lactic acid-glycolic acid co-polymers; and

a composition that forms a gel when mixed with water consisting essentially of:

a cryoprotecting agent;

a gelling agent; and

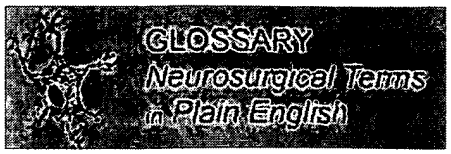
a surfactant;

wherein a second compartment contains a unit dosage of said water for injection.

APPENDIX III

Bone Wax

Bone wax



Bone hemostasis after twist drilling, burr perforation, or craniotomy.

Bone wax - neurosurgical instruments

Pieces of bone wax (circled in yellow). Three are white, the fourth is elongated and mixe with blood after it was shaped by the surgeon in the surgical field.

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APPENDIX IV

Aldrich Catalogue, page 392

mp 209-212° *IRRITANT*

C1,340-8 Carboxymethoxylamine hemihydrochloride, 98% [*2921-14-4*] [(aminooxy)- 250mg 13.00
acetic acid hemihydrochloride] $(H_2NOCH_2CO_2H)_2 \cdot HCl$ FW 218.59 mp 156°(dec.) 1g 35.70
FT-IR **1**(1),591C *Safety* **2**,691B *R&S* **1**(1),659L *RTECS*# AF3150000 *IRRITANT* 10g 209.00
HYGROSCOPIC
Undergoes condensation with aldehydes[1] and ketones[1,2] to form oximes. (1)
Tetrahedron Lett. **1993**, *34*, 4347. (2) *Farmaco* **1991**, *46*, 887.

29,855-7 7-(Carboxymethoxy)-4-methylcoumarin, 97% [*64700-15-8*] FW 234.21 ..... 250mg 22.00
mp 206-208° *FT-NMR* **1**(2),1320A *Safety* **2**,691C *R&S* **1**(2),1947H *IRRITANT* 1g 60.30

37,158-0 3-(Carboxymethylaminomethyl)-4-hydroxybenzoic acid, tech., 85% 1g 15.40
[*55739-39-4*] $HO_2CCH_2NHCH_2C_6H_3(OH)CO_2H$ FW 225.20 mp 220°(dec.) 10g 84.20
FT-NMR **1**(2),1133A *R&S* **1**(2),1813J *IRRITANT*

37,163-7 3-(Carboxymethyl)benzothiazolium bromide, 96% [*74385-09-4*] FW 274.14 ..... 10g 26.20
mp 250°(dec.) *FT-NMR* **1**(3),210A *R&S* **1**(2),2457K *IRRITANT* 50g 86.70

32,306-3 Carboxymethyl cellulose, sodium salt [*9004-32-4*] mp >300° 25g 15.10
★ *Merck Index* **13**,1840 *Safety* **2**,691D *R&S* **1**(2),3161E *RTECS*# FJ5950000 1kg 55.70
Viscosity 3,000-6,000 cps (1% aqueous solution) 2.5kg 124.90
Thickener

36,038-4 Carboxymethyl cellulose, sodium salt, ultra low viscosity [*9004-32-4*] 500g 41.50
★ Viscosity 10-55 cps (4% soln. in H_2O, 25°C) 1kg 55.70

41,927-3 Carboxymethyl cellulose, sodium salt [*9004-32-4*] 100g 22.40
★ Average M_w *ca.* 90,000, DS = 0.7 1kg 49.00

41,931-1 Carboxymethyl cellulose, sodium salt [*9004-32-4*] 100g 22.40
★ Average M_w *ca.* 250,000, DS = 0.7 1kg 49.00

41,930-3 Carboxymethyl cellulose, sodium salt [*9004-32-4*] 100g 22.40
★ Average M_w *ca.* 250,000, DS = 0.9 1kg 49.00

41,928-1 Carboxymethyl cellulose, sodium salt [*9004-32-4*] 100g 22.40
★ Average M_w *ca.* 250,000, DS = 1.2 1kg 49.00

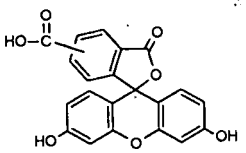
41,933-8 Carboxymethyl cellulose, sodium salt [*9004-32-4*] 100g 22.40
★ Average M_w *ca.* 700,000, DS = 0.9 1kg 49.00

Carboxymethyl(2-hydroxyethyl)ethylenediglycine, see (2-Hydroxyethyl)-ethylenediaminetriacetic acid

(Carboxymethylimino)bis(ethylenenitrilo)tetraacetic acid, see D9,390-2, Diethylenetriaminepentaacetic acid page 650

38,622-7 2-[2-[3-(Carboxymethyl)-5-methyl-2(3*H*)-benzothiazolylidenemethyl]-1-butenyl]-3-ethyl-5-methylbenzothiazolium hydroxide, inner salt 250mg 56.20
[*52749-17-4*] FW 450.62 mp 160°(dec.) λ*max* 522nm *R&S* **1**(2),2819I
Dye content ~90%

15,274-9 1-(Carboxymethyl)pyridinium chloride, 98% [*6266-23-5*] FW 173.60 ..... 100g 24.70
★ mp 185-189°(dec.) *FT-NMR* **1**(3),316B *FT-IR* **1**(2),784B *Safety* **2**,692C *R&S* **1**(2),2537I
IRRITANT HYGROSCOPIC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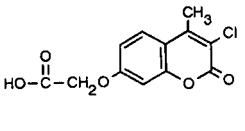
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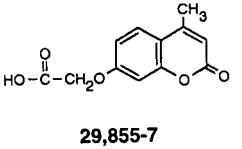
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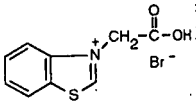
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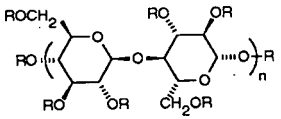
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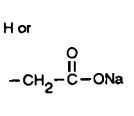

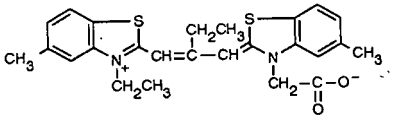
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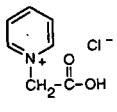

15,274-9

IRRITANT

3-Carboxy-4-nitrophenyl disulfide, see D21,820-0, 5,5'-Dithiobis acid) page 794

18,662-7 4-Carboxyphenoxyacetic acid, tech., 94% [*19360-67-9*] (α-carb acid) $HO_2CC_6H_4OCH_2CO_2H$ FW 196.16 *Beil.* **10**,158 *FT-IR* **1**(2),155

45,676-4 3-Carboxyphenylboronic acid [*25487-66-5*] $HO_2CC_6H_4B(OH)_2$ F mp 243-247° *Beil.* **16**(3),1283 *RTECS*# CY8750000 *IRRITANT*
Contains varying amounts of anhydride

45,677-2 4-Carboxyphenylboronic acid [*14047-29-1*] $HO_2CC_6H_4B(OH)_2$ F mp 220°(dec.) *RTECS*# CY8925000 *IRRITANT*
Contains varying amounts of anhydride

36,774-5 *N*-(2-Carboxyphenyl)glycine, 97% [*612-42-0*] $HO_2CC_6H_4NHCH_2C$
★ mp 218°(dec.) *Beil.* **14**,348 *FT-NMR* **1**(2),1181A *R&S* **1**(2),1841I *IRRI*

3-(2-Carboxyphenyl)propionic acid, see 40,646-5, 2-Carboxybe acid page 391

53,155-3 3-(4-Carboxyphenyl)propionic acid, 97% [*70170-91-1*] HO_2CC_6
NEW FW 194.18 mp 289-293° *IRRITANT*

56,015-4 1-(3-Carboxyphenyl)-2-thiourea, 97% [*37182-75-5*] $H_2NC(S)NHC$
NEW FW 196.22 mp 187-191°

53,237-1 Carboxypolystyrene, 100-200 mesh, 1% cross-linked .....
NEW Typical loading 0.5-1.5 mmol/g

53,239-8 Carboxypolystyrene, 100-200 mesh, 1% cross-linked .....
NEW Typical loading 1.6-3.0 mmol/g

Carboxypolystyrene, see also 55,517-7, ScavengePore® benzoi

2-(3-Carboxypropyl)-4,4-dimethyl-2-tridecyl-3-oxazolidinyloxy f 25,363-4, 5-DOXYL-stearic acid, free radical page 807

3-Carboxypropyl disulfide, see C1,560-5, 4,4'-Dithiodibutyric aci

40,324-5 (3-Carboxypropyl)trimethylammonium chloride, tech. [*6249-56* betaine hydrochloride, deoxycarnitine hydrochloride) $HO_2C(CH_2$ FW 181.66 mp 220°(dec.) *Beil.* **4**(1),506 *FT-NMR* **1**(1),878B *FT-IR* **1**(1) *R&S* **1**(1),659D *RTECS*# BP3850000 *IRRITANT HYGROSCOPIC*

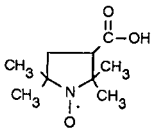
34,972-0 (3-Carboxypropyl)triphenylphosphonium bromide, 98% [*17857* $HO_2C(CH_2)_3P(C_6H_5)_3Br$ FW 429.30 mp 244-247° *IRRITANT*

25,332-4 3-Carboxy-PROXYL, free radical [*2154-68-9*](3-carboxy-2,2,5,5-t
★ pyrrolidinyloxy, free radical) FW 186.23 mp 200°(dec.) *FT-IR* **1**(2),9 *R&S* **1**(2),2669C *RTECS*# UY6705500
Spin-label. The anionic form has been used to determine distribution coe neutral solubilizates in anionic micelles. *J. Chem. Soc., Faraday Trans.* 1

30,380-1 4-Carboxypyridinium dichromate, 97% [*104316-83-8*] FW 464.23 *R&S* **1**(2),2539F *CANCER SUSPECT AGENT OXIDIZER*

38,200-0 4-Carboxy-TEMPO, free radical, 97% [*37149-18-1*] (4-carboxy-2,2 tetramethylpiperidinyloxy free radical) FW 200.26 mp 186°(dec.)

2-(14-Carboxytetradecyl)-2-ethyl-4,4-dimethyl-3-oxazolidinyloxy see 25,359-6, 16-DOXYL-stearic acid, free radical page 807


25,332-4

38,